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The abuse potential of two novel synthetic cathinones with modification on the alpha-carbon position, 2-cyclohexyl-2-(methylamino)-1-phenylethanone (MACHP) and 2-(methylamino)-1-phenyloctan-1-one (MAOP), and their effects on dopaminergic activity

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ABSTRACT

The recreational use of synthetic cathinones has dramatically increased in recent years, which is partly due to easy accessibility and ability of synthetic cathinones to exert rewarding effects similar to cocaine and methamphetamine. Many synthetic cathinones have already been scheduled in several countries; however, novel and diverse synthetic cathinones are emerging at an unprecedented rate, often outpacing regulatory processes. Recently, designer modifications of the basic cathinone molecule are usually performed on the alpha-carbon position. In this study, we designed and synthesized two novel synthetic cathinones with substituents on alpha-carbon position, [1] 2-cyclohexyl-2-(methylamino)-1-phenylethanone (MACHP), and [2] 2-(methylamino)-1-phenyloctan-1-one (MAOP). Then, we evaluated their rewarding and reinforcing effects through the conditioned place preference (CPP) in mice and self-administration (SA) test in rats. Locomotor activity was also assessed in mice during daily MACHP or MAOP treatment for 7 days and drug challenge. qRT-PCR analyses were conducted to determine their effects on dopamine-related genes in the striatum. MACHP and MAOP produced CPP at 10 and 30 mg/kg. In the SA test, MACHP (1 mg/kg/infusion), but not MAOP, was self-administered. Both MACHP and MAOP induced locomotor sensitization in mice. qRT-PCR analyses showed that MACHP and MAOP reduced dopamine transporter gene expression in the striatum. These data indicate that MACHP and MAOP may have rewarding properties, which might be attributed to their ability to affect the dopaminergic activity. These findings may be useful in predicting the abuse potential and hasten the regulation of future cathinone entities with similar modifications.

1. Introduction

Synthetic cathinones are beta-ketone compounds derived from cathinone, the active stimulant in the khat plant (*Catha edulis*), that possess psychostimulant, hallucinogenic, and entactogenic properties (Banks et al., 2014). They are sold to costumers via the Internet or head shops or distributed in the streets as “plant food” or “research chemicals” to circumvent the drug laws banning their sale as products for human consumption (Coppola and Mondola, 2012; German et al., 2014). The use of these synthetic compounds has recently gained popularity among recreational drug users. In consequence, this phenomenon has become a growing worldwide problem (Brandt et al., 2011; Spiller et al., 2011). Legislative laws that banned the use of synthetic cathinones have been enacted; however, sources for novel synthetic cathinones are still increasing, making the application of drug laws difficult. Although the newly introduced compounds have similar behavioral or neurological effects to their respective analogs, they are still not covered by drug laws because of their divergent chemical structures (Karila et al., 2015; Prosser and Nelson, 2012).

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Modifications to the chemical structure of cathinone or its analogs can create a wide range of designer drugs. According to the European Monitoring Center for Drugs and Drug Addiction, there were over 80 synthetic cathinone derivatives detected between 2005 and 2014 (European Monitoring Centre for Drugs and Drug Addiction, EMCDDA, 2015). In an unsubstituted cathinone molecule, there are different areas in the molecule where designer modifications (introduction of substituents) can occur, one of these is the alpha-carbon position (Abiedalla et al., 2012; Paillet-Loilier et al., 2014). Recently, there has been an increasing number of synthetic cathinones with modifications on the alpha-carbon position in the drug market which are being recreationally used by humans, such as pentedrone and buphedrone (Maheux and Copeland, 2012; Paillet-Loilier et al., 2014; Zuba et al., 2013). These synthetic cathinones usually have alkyl chain substituents at alpha-carbon that range from methyl to propyl. Some of these substances were reported to produce psychopharmacological effects similar to known psychoactive drugs like methamphetamine and cocaine (Hwang et al., 2015; Marusich et al., 2012; Oh et al., 2016). They have also been found to influence dopaminergic neurotransmission in the brain reward circuit, a brain system implicated for drug reward and reinforcement (Hwang et al., 2015; Oh et al., 2016; Watterson and Olive, 2014). Furthermore, these substances induce conditioned place preference (CPP) and self-administration (SA) in rodents. Based on these observations, it appears that synthetic cathinones with alpha-carbon substituents could produce addictive effects and may have the potential for abuse.

As part of the continuing effort of the Drug Abuse Research Institute of Korea (DARC) to hasten the regulation of new synthetic cathinones and to predict abuse potential of future synthetic cathinone entities, the present study designed and synthesized 2-cyclohexyl-2-(methylamino)-1-phenylethanone (MACHP) and 2-(methylamino)-1-phenyloctan-1-one (MAOP), two novel synthetic cathinones with cyclohexyl and n-hexyl substituents at the alpha-carbon position, respectively (Fig. 1). Thereafter, we performed the CPP and SA tests, two of the widely used animals' models for drug addiction, to determine whether MACHP and MAOP have rewarding and reinforcing properties. We also examined if these substances could induce locomotor sensitization during 7 days of treatment and drug challenge following 7 days of abstinence. In addition, we evaluated the effects of MACHP and MAOP on the dopaminergic activity by analyzing the expression of dopamine-related genes in the brain (i.e. striatum) of the mice through quantitative real-time polymerase chain reaction (qRT-PCR).

2. Materials and methods

2.1. Animals

All animals were obtained from Hanlim Animal Laboratory Co. (Hwasung, Korea). Male ICR (6 weeks) mice, weighing 22 to 27 g, were used in the CPP test, locomotor sensitization test, and qRT-PCR analyses. They were housed 6–8 per cage. Male Sprague-Dawley rats (6 weeks), weighing 200–300 g, were used for the SA test and housed individually. All animals were kept in a temperature- (22 ± 2 °C) and humidity-controlled (55 ± 5%) animal room on a 12/12H light/dark (07:00–19:00H light) schedule. They were acclimatized to the laboratory setting for five days prior any experiments. They had free access to food and water during acclimatization and experiments, except for the rats during lever training and SA sessions. All tests were performed in accordance with the Principles of Laboratory Animal Care (NIH Publication No. 85-23, revised 1985) and the Animal Care and Use of Guidelines of Sahmyook University, Korea.

2.2. Drugs

2.2.1. 2-cyclohexyl-2-(methylamino)-1-phenylethanone (MACHP)

MACHP was synthesized from benzene as described previously with minor modifications (Carroll et al., 2009; Power et al., 2011). Benzene was treated 2-cyclohexylacetyl chloride and then brominated with bromine to give 2-bromo-2-cyclohexyl-1-phenylethanone. The resulting compound was reacted with methylamine to afford MACHP hydrochloride. Its structure was confirmed by the following spectroscopic analyses. ^{1}H NMR (400 MHz, CD3OD) δ 8.09–8.07 (m, 2H), 7.78 (m, 1H), 7.65–7.61 (m, 2H), 5.12 (d, J = 3.6 Hz, 1H), 2.73 (s, 3H), 2.02 (m, 1H), 1.91–1.63 (m, 5H), 1.37–0.91 (m, 5H); ^{13}C NMR (100 MHz, CD3OD) δ 188.5, 142.6, 138.4, 135.9, 129.3, 68.7, 53.2, 51.1, 30.8, 23.0, 22.7, 21.6, 18.3, 13.1; HR-Mass calcd for (C15H22NO+) 232.1696, found 232.1714.

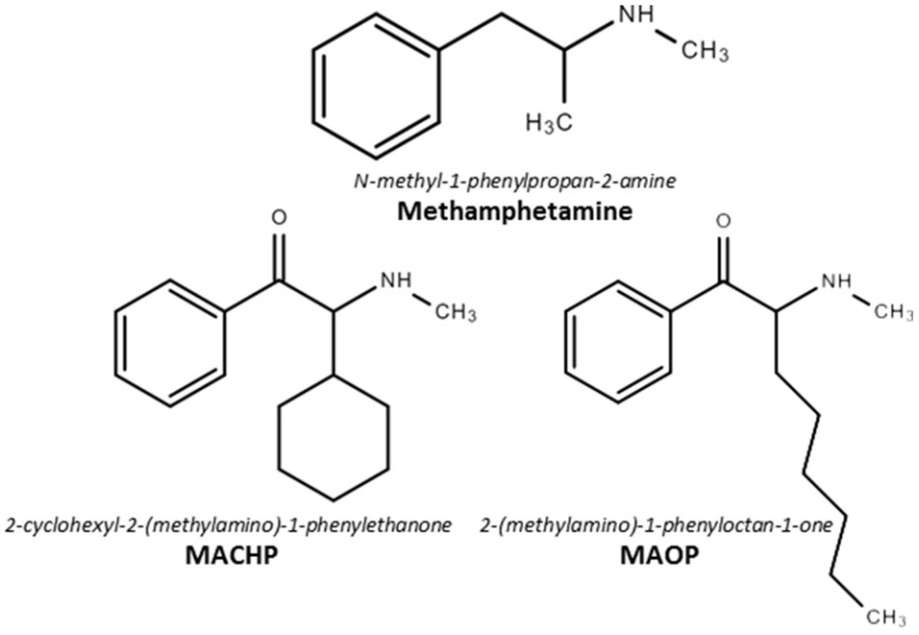

Fig. 1. Chemical structures of methamphetamine, 2-cyclohexyl-2-(methylamino)-1-phenylethanone (MACHP), and 2-(methylamino)-1-phenyloctan-1-one (MAOP).